SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Agenerase. This scientific discussion has been updated until 1 September 2004. For information on changes after this date please refer to module 8B.

1. Chemical pharmaceutical and biological aspects

Composition

Soft capsules

The two strengths of Agenerase soft capsules (50 mg or 150 mg of amprenavir) have the same relative composition and are identified by different imprints. Amprenavir free base is dissolved in a vehicle containing d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS, a derivative and source of vitamin E), macrogol 400 and propylene glycol. The capsules are contained in white opaque HDPE bottles with child-resistant closure. The packaging system for the 150 mg soft capsules has been reinforced through addition of LDPE foam filler. Satisfactory certificates have been provided for gelatine to confirm the absence of risk of transmission of TSE.

Oral solution

To provide an acceptable dosage form for the paediatric population, an oral solution containing 15 mg/ml amprenavir has also been developed. The oral solution, which has a grape flavour, is provided in white opaque HDPE bottle with polypropylene child-resistant closure. Amprenavir free base is dissolved in the same solubilising excipients as used in the soft capsules. A 20-ml polypropylene dosing cup is supplied in each pack.

As further discussed in part 4 of this document, the soft capsules and the oral solution are not bioequivalent and therefore can not be interchangeable on a milligram per milligram basis.

Active substance

Amprenavir contains three stereogenic centers and is a single enantiomer with the (3S), (1S, 2R) configuration. The absolute configuration is ensured by control tests of the starting materials and the synthetic process retains this configuration.

Different polymorphs of amprenavir free base have been identified, but Form V is thermodynamically the most stable at normal temperatures and is not hygroscopic. This polymorph is therefore used for the product intended for marketing.

The route of synthesis of amprenavir has been modified along the development of the product with respect to the use of solvents at different steps of the process in order to ensure the production of Form V. Considering that the differences are minor, no impact on the impurity profile and/or stability of amprenavir is expected. Potential drug-related impurities arising from the route of synthesishave been adequately discussed.

The synthesis of the active substance has been adequately described. The control of the starting materials and the intermediates of synthesis enables a reproducible quality of the active substance, especially with regard to its chiral purity. The specifications, including identification of amprenavir Form V, and the routine tests performed are adequate to ensure the quality of the active substance. The potential impurities have been toxicologically qualified. Batch analyses for five batches of amprenavir, including two production scale size, manufactured in accordance with the proposed commercial process meet the proposed specifications.

A retest period of 24 months for the active substance at or below 30°C is supported by the stability data provided up to 18 months (3 production scale batches manufactured with an early synthetic route) and 12 months (3 production scale batches produced according to the commercial route).

Other ingredients

Most of the ingredients entering in the composition of the soft capsule or oral solution meet pharmacopoeial requirements. TPGS has a GRAS status. The tolerance of the vehicle has been evaluated in the toxicological studies and it was not excluded that immunological reactions could be induced by PEG 400.

The packaging material is standard. The accuracy and reproducibility of the dosing device, a 20 ml measuring cup, have been adequately shown.

Product development and finished product

Soft capsules

Amprenavir has a low solubility in water and a low bioavailability. During the development, the choice of the form and of the vehicle used was optimised with respect to bioavailability and rapid absorption by the body. Initially, the only available crystalline form of amprenavir was the mesylate salt, used during the early clinical trials. With the discovery of the polymorph V, which is thermodynamically more stable but has a lower solubility, a reformulation was necessary. The final formulation including the selection of each excipient, the fill solution and capsule shell development, as well as the process development, has been adequately justified.

A hard capsule formulation containing amprenavir mesylate and different soft capsule formulations, containing various amounts of TPGS, have also been used during the clinical trials.

The manufacturing process of the capsules, which uses standard soft capsules manufacturing technology, has been adequately described. In-process controls are sufficient to ensure a reproducible quality. Validation data on three production scale batches, of each strength of the soft capsules, showed that the manufacturing process produces a uniform and homogeneous product that will consistently meet the specifications proposed for the finished product. The acceptance limits established for the degradation product in the finished product are supported by toxicological studies.

Oral solution

The formulation including the selection of each excipient, artificial sweeteners as well as the process development, has been adequately justified. There was some concerns, however, with the high amount of propylene glycol used in the oral solution (550 mg/ml), resulting in a daily intake of this excipient in excess to the acceptable limit defined by FAO/WHO, especially since the oral solution is intended to be used in children. The issue has therefore been further addressed from a toxicological and clinical point of view. The lack of a preservative in the formulation has been adequately justified.

Two different formulations of the oral solution, which slightly differ with respect to flavour and pH have been used during the clinical trials.

The manufacturing of the oral solution is under control. The following key steps have been identified: solubilisation of amprenavir, pH adjustment, filtering and filling. Data from three batches manufactured using the commercial process meet the specifications. The acceptance limits established for the degradation product in the finished product are supported by toxicological studies.

Stability of the product

Soft capsules

Stability data have been provided up to 18 months (25°C/60 % RH) for the two strengths (three batches of each strength containing the active substance synthesised with an earlier process). No crystal formation has been observed during storage. The results are within the specifications and therefore 24 months shelf life is acceptable when the soft capsules are stored below 30°C. The shelf life was subsequently extended to 3 years.

Oral solution

Stability data are provided up to 12 months with three production scale batches. Supportive data up to 18 months obtained with an earlier formulation, which differed in terms of pH and flavours have also

been provided.The three production scale batches contain amprenavir synthesised with the commercial process and the supportive batches contain amprenavir synthesised with an early process. The results are within the specifications and therefore 24 months shelf life is acceptable. The shelf life was subsequently extended to 3 years.

2. Toxico-pharmacological aspects

Pharmacodynamics

Amprenavir is a non-peptidic, competitive inhibitor of the HIV protease. It blocks the ability of the viral protease to cleave precursor polyproteins necessary for viral replication. Amprenavir is a selective inhibitor of HIV-1 and HIV-2 replication.

- Antiviral activity

The *in vitro* investigation of the antiviral activity is limited but reveals that amprenavir is active against a broad range of HIV-1 strains, including clinical strains. The concentration that inhibits 50 % of replication of HIV-1_{IIIB} (IC50 value) ranged between 0.012 μM and 0.08 μM. In subsequent clinical studies, 68 clinical isolates from geographically different regionswere tested at baseline for susceptibility to amprenavir with a range of IC50 values between0.003 - 0.204 μM (0.001 – 0.09 μg/ml). Amprenavir was shown to inhibit the protease with the respective inhibition constants (Ki) of 0.6 nM for HIV-1 and 19 nM for HIV-2. The IC50 values of amprenavir for human aspartyl protease have not been determined but for pepsine and cathepsin D the Kis were 1000-fold higher and for renin 90-fold higher than the respective values for HIV-1 and HIV-2. Amprenavir has a therapeutic index of > 500 based on *in vitro* assays. The antiviral activity of amprenavir is influenced by protein binding and inhibitory levels increase by 2 to 5 fold in the presence of plasma proteins, especially alpha-1-acid glycoprotein. The major metabolites of amprenavir have no antiviral activity. The antiviral activity of amprenavir has not been evaluated *in vivo* in animal studies.

In vitro data indicated a synergistic activity of amprenavir in combination with zidovudine, didanosine, abacavir and saquinavir and an additive activity with indinavir, ritonavir and nelfinavir. Amprenavir did not inhibit any other human pathogens at concentrations up to 100 μM.

- Resistance profile

In vitro the key protease mutation associated with resistance to amprenavir was at position 50 (I50V, isoleucine to valine) that resulted in 3-fold reduction in susceptibility. On continued passage in the presence of amprenavir, further mutations arose within the active site flap region, first at residue 46 (M46I/L, methionine to isoleucine/leucine) which produced a double mutant and, second, a mutation at residue 47 (I47V, isoleucine to valine) which produced a triple mutant. The double and the triple mutations resulted in a 3 to 7-fold and 10 to 20-fold reductions in sensitivity to amprenavir, respectively. This triple mutant has not been observed with any of the other protease inhibitors available.

In vitro variants resistant to amprenavir were still very sensitive to saquinavir, indinavir and nelfinavir but showed 3 to 5-fold reduced susceptibility to ritonavir. Further *in vitro* studies suggested that concomitant therapy with amprenavir and saquinavir or indinavir may delay the acquisition of mutationsassociated with resistance to amprenavir. Conversely the combination of ritonavir and amprenavir produced dual resistance. Many PI resistant variants were still sensitive to amprenavir. Little cross-resistance has been observed with amprenavir selected resistant variants and other PIs suggesting a potential PI salvage therapy following amprenavir failure. The clinical consequences of these results are currently unclear.

- General and safety pharmacology programme

There was no evidence of any marked effects of amprenavir on the major organ systems in mice, rats and dogs at doses up to 1000 mg/kg. Amprenavir showed a weak β-1 antagonistic activity. In addition, at concentrations of 10 μM, amprenavir had significant negative chronotropic and inotropic effects in

spontaneously beating guinea-pig atria. These effects have not been observed in other *in vitro*, *in vivo* and clinical studies and therefore are considered of no clinical relevance.

Pharmacokinetics

The pharmacokinetic profile of amprenavir has been determined using validated testing methods in several species (mouse, rat, rabbit, dog and cynomolgous monkey in early studies) after single and multiple dose administration.

Absorption and distribution

Amprenavir, when appropriately formulated, was rapidly and well absorbed after single oral administration with T_{max} values of approximately 1 hour in rats and dogs. Bioavailability estimates for amprenavir were calculated in rats and dogs with formulations similar to the soft capsule formulation used in clinical studies. With single doses (11 mg/kg in rats and 25 mg/kg in dogs) similar to that following single administration in humans (24 mg/kg based on a dose of 1200 mg to a 50 kg human), the estimated bioavailability was 40 % in rats and 98 % in dogs. At doses of 65 and 175 mg/kg in dogs, bioavailability decreased to 66% and 35% respectively. The proportion of the dose in rat or human faeces, excreted as the parent compound after administration of radiolabelled amprenavir, was less than 13 % suggesting that oral bioavailability was limited by pre-systemic clearance and not by absorption.

Estimates of C_{max} and AUC generally increased in a dose-dependent, but not dose-proportional manner after administration of amprenavir to rats and dogs. After multiple oral dose administration of amprenavir to rats with doses ranging from 50 to 1000 mg/kg/day, AUC values in dose groups greater than 50 mg/kg/day decreased by 30% to 70% after day 1, and remained generally stable thereafter. After multiple oral dose administration of greater than 50 mg/kg/day amprenavir to dogs, however, AUC values increased after the first dose, and remained generally stable with continued dosing.

Protein binding at the therapeutic concentration of 10 µg/ml was 81 % and 82 % in rat and dog respectively, compared with greater than 90 % in humans. Protein binding decreased with increasing amprenavir concentrations. The partitioning of amprenavir into erythrocytes was low but increased with increasing amprenavir concentrations, reflecting the higher amount of unbound drug. In whole-body autoradiography studies in rats, amprenavir was widely distributed with high levels found in the gastrointestinal tract and in the bile duct. However the ability of amprenavir to penetrate the blood-brain barrier appeared to be minimal in this species. Amprenavir crossed the placenta and distributed into milk, a finding which has been adequately addressed in Section 4.6 of the Summary of Product Characteristics.

Metabolism and elimination

In rats and dogs, the mean percentages of administered dose recovered in faeces were 104 % and 84 % respectively. Amprenavir was extensively metabolised, with the cytochrome P450 isozyme CYP3A sub-family primarily responsible for the production of the oxidative metabolites. Twenty-four metabolites of amprenavir have been characterised in rats and dogs. Excretion of unchanged amprenavir accounted approximately for 13 % of the dose in rats, and 52 % of the dose in dogs. The major radiolabelled component excreted in the faeces of rats (51 % of the radiocarbon) and humans (62 % of the radiocarbon) was a metabolite resulting from di-oxidation of the tetrahydrofuran moiety. A second metabolite (6 % of the radiocarbon in rats and 32 % of the radiocarbon in humans) was a metabolite resulting from di-oxidation of the tetrahydrofuran moiety and an additional oxidation of the aniline portion of the molecule. Glucuronides and acetylated metabolites of parent compound have been identified, showing that amprenavir is a substrate for uridine-diphosphate glucuronosyl transferase (UDPGT) and N-acetyl transferase. All of the metabolites identified in humans have also been seen in rats or dogs, but the rat metabolic profile appeared more similar to the human metabolic profile. Amprenavir was eliminated mono-exponentially with a half-life of 1to 2 hours in rats and dogs compared to 7 to 10 hours in humans.

Amprenavir is an inhibitor of human and rat microsomal activity CYP3A4 at clinically relevant concentrations; a comparison of amprenavir and other HIV protease inhibitors showed the potency of CYP3A4 inhibition to be the following (in declining potency): ritonavir >> indinavir ≅ nelfinavir ≅

amprenavir > saquinavir. Metabolic interactions are mostly likely to occur with substances that affect, or are affected by, CYP3A4 and UDPGT. Co-administration of amprenavir and abacavir in rats and humans had no apparent effect on systemic exposure of either compound.

In dogs there was no effect on C_{max} or T_{max} values of amprenavir after co-administration with saquinavir or ritonavir. Saquinavir had no effect on amprenavir AUC, but ritonavir increased amprenavir AUC values by 25 %. Co-administration of amprenavir and cimetidine resulted in a moderate decrease (17 %) in amprenavir AUC values and a small decrease (8 %) in cimetidine AUC values.

There were no significant sex differences in pharmacokinetic parameters. Systemic exposure to amprenavir was similar after oral dosing of pregnant and non-pregnant rats; plasma concentrations of amprenavir were higher after oral administration in juvenile rats compared to mature rats, probably due to underdeveloped drug metabolising capacities in juvenile animals.

Toxicology

A conventional toxicity programme has been conducted in compliance with Good Laboratory Practices. Studies have been performed both with amprenavir mesylate and free base contained in a formulation equal or at least similar to the clinical soft capsule formulation or the paediatric liquid formulation. The oral route was mostly used since it is the proposed clinical route of administration. The oral bioavailability of amprenavir free base was good in the dog, adequate in the rat and poor in the rabbit. For amprenavir mesylate, oral bioavailability was adequate in the rat and poor in the cynomolgus monkey. Due to the fact that estimates of C_{max} and AUC were sub-proportional to dose at the dose levels used in animal toxicity studies, animals were dosed twice daily to maximise exposures. At the end of the long term rat and dog studies, at the high dose level AUC values were approximately 2.3 to 2.8 and 5.4 to 11.2 times the human AUC, at the proposed therapeutic dose, respectively (the median AUC in humans at the therapeutic dosage of 1200 mg bid was approximately 37 μg.h/ml).

Only one early study has been carried out on the cynomolgus monkey since the dog was shown to be a better pharmacokinetic model for amprenavir in humans.

Single dose toxicity: After oral dosing, all rats survived a maximum dose of 3000 mg/kg with minimal signs and mice died at doses of ≥ 1000 mg/kg after salivation, labored breathing, and prostration. Intravenous doses of ≥ 100 mg/kg in the rat and ≥ 75 mg/kg in the mouse produced death with preceding signs of labored breathing, prostration and convulsions. Ataxia noted in amprenavir and control animals was considered related to the PEG 400 dosing vehicle.

Repeated dose toxicity : In the 6-month rat study, doses ranged from 50 to 750 mg/kg/day. In the 6 and 12 months dog studies, the high dose was reduced to 225 mg/kg/day due to severe clinical signs of emesis, weight loss and dehydration observed with higher doses.

The liver was the primary target organ for toxicity of amprenavir free base in both species. Dose related increases in liver weight and correlated hepatocellular hypertrophy were seen in most studies. Histopathological signs of toxicity, such as hepatocyte pigmentation and necrosis, were also noted at higher doses. The concomitant finding of increased liver and thyroid weights, and hepatocyte and thyroid follicular hypertrophy in both rats and dogs, were most likely the result of induction of liver drug metabolising enzymes by amprenavir. In terms of laboratory findings, AST and ALT activities increased at all doses in male rats, but inversely proportional to dose. There was also an increase during the recovery period. Although the cause of this effect has not been elucidated, no significant liver toxicity that could involve safety concerns in human use, was found during clinical studies.

In the dog, reductions in red cell indices were found in all studies, but were reversible during the recovery period. These haematological variations are considered to be of no clinical relevance since no significant effects on erythroid paramaters have been reported during the clinical studies.

In four studies where amprenavir was administered daily for approximately one month to rats in different formulations starting at age 4 days, a high percentage of pups died due to acute toxicity. A high mortality response was also reported in the vehicle control group. The possibility that amprenavir may be more toxic in very young animals (may be due to immaturity of their metabolising enzymes) which may be influenced by the vehicle (propylene glycol, PEG 400), is unlikely to be of any

consequences for patients four years old and over. These results have been reflected in the Summary of Product Characteristics.

Genotoxicity: Amprenavir mesylate and free base are neither mutagenic nor clastogenic in a standard battery of *in vivo* and *in vitro* genotoxic tests.

Carcinogenicity: the studies performed in rodents was l ongoing at time of Marketing Authorisation.. Provision of the results is part of the follow-up measures to be fulfilled by the applicant.

Final reports of the two-year carcinogenicity studies in rats and mice were submitted to fulfil the commitment as a follow-up measure.

In **mice**, there was a treatment-related statistically significant increase in the incidence of hepatocellular adenomas in male at the high dose. A high incidence of hepatocellular carcinoma was seen in all male APV-treated groups although the increase was not statistically significantly different from male control mice and is within the range of historical controls for this finding at the test facility. In females, an increase in incidence of hepatocellular adenomas at the medium dose was reported and was not statistically different from controls and also was within the range of historical controls at this laboratory.
APV–related liver changes were seen in all treated groups, consistent with the toxicity profile of APV from the toxicity studies.

In **rats**, the incidence of hepatocellular adenomas was increased in males at the medium and high dose. A similar finding was not seen in females. According to the Expert of the MAH, although the incidence of hepatocellular adenomas in males was higher than in either control group, it was within the historical control range of the test facility.
The mechanism for the hepatocellular adenomas and carcinomas found in these studies has not been elucidated. Although the incidences for hepatocellular carcinomas were not statistically significantly different from controls an increase in the incidence was reported with a low safety margin and the clinical relevance in humans is unknown.
Also, it should be considered that APV-related changes were seen in the liver during the toxicology program in rodents and dogs. Therefore, the liver can be considered as a target organ for toxicity.

The Marketing Authorisation Holder proposed an adequate statement to be added to section 5.3 of the SPC.

Reproduction toxicity:

Orally administered amprenavir mesylate or free base was evaluated for effects on fertility, embryo-foetal and perinatal development.

Amprenavir had no effect on the mating performance and fertility of male and female rats. However, amprenavir was shown to cross the placenta.

In rats, minor abnormalities indicating developmental delay were identified. Some evidence for embryo-foetal toxicity (reduced ossification of the skull bones) was found in the group receiving the highest dose (750 mg/kg/day), which gives systemic exposure approximately 2.3 times the exposure in humans. Females showed a significant dose dependent increase in placental weights.

Studies in rabbits showed that pregnant rabbits have poor tolerance to amprenavir and its vehicle compared to non-pregnant rabbits. Only limited systemic exposure was therefore achieved in pregnant rabbits which makes conclusions difficult to draw. Results carried out with another more suitable second species will be submitted once available.

Post natal development study in rats showed that male and female pups from dams that received 750 mg/kg/day had significantly lower mean body weights. Amprenavir has also been shown to be excreted in rat milk. On the basis of these results, amprenavir should not be administered in pregnant women unless potential benefit outweighs the potential risk to the foetus, as indicated in the Summary of Product Characteristics. In addition, breast-feeding is not recommended.

As a follow up measure following Marketing Authorisation, it was stated that another more suitable species to study the effects of APV should be considered. According to the follow-up measure, the

Marketing Authorisation Holder submitted in December 2000 a pilot developmental toxicity study in pregnant CD-1 BR mice, to determine if the mouse is a suitable species in which to conduct a subsequent developmental toxicity study. Several findings (variation of tarsal flexure, cleft palate, ablepharia) were reported, although differences were not statistically significant related to controls. The Applicant considered that the mouse was not likely to offer any new information about the teratogenic potential of amprenavir and no further studies were planned to evaluate the reproductive toxicity of amprenavir.

Therefore, although the lack of a suitable second species for reproductive toxicity does not alter the safety assessment, the CPMP required that the currently approved SPC was updated with reference to the data in the mouse alongside data in the rat and the rabbit.
Local tolerance: amprenavir free base was not a sensitiser and not an irritant to the skin, but was a slight irritant to the rabbit eye.

Environmental risk assessment: no toxicological risk for the environment with amprenavir is foreseen.

Other toxicity: The toxicity of amprenavir free base in combination with abacavir sulphate was investigated in rats. High dose of amprenavir and abacavir at exposures (in terms of AUC) equivalent to 35 (abacavir) and 3.5 (amprenavir) times the exposures in humans at the therapeutic dose (i.e 530 and 750 mg/kg/day, respectively) caused increased heart weight. This effect was not accompanied with significant changes in histopathology but was still present in females after recovery period showing that this effect seems to be irreversible. This effect was not acheived with either of the products administered alone.

Impurities: Results from three specific oral impurity studies showed that impurities at a concentration of at least 15 times greater than the current specifications did not change the established toxicity profile or mutagenic potential of amprenavir.

3. Clinical aspects

The clinical programme consists of fifteen pharmacokinetic studies, two dose ranging studies and two phase III clinical trials to support the indication of amprenavir in adults. Five supportive phase I/II studies have also been submitted. In addition, three pharmacokinetics studies, one phase II and one phase III studies have been conducted to support the indication in children. All the clinical trials have been performed according to GCP standards and agreed international ethical principles. The clinical programme intended to evaluate the efficacy and safety of amprenavir generally in combination therapy, with NRTIs both in antiretroviral naive and experienced patients including PI naive patients. Double, triple and quadruple therapies with amprenavir have been evaluated but not all possible combinations have been studied.
The approved indication is the following:

> *Agenerase is indicated for the treatment of protease inhibitor experienced HIV-1 infected adults and children above the age of 4 years, in combination with other antiretroviral agents. The choice of amprenavir should be based on individual viral resistance testing and treatment history of patients.*
>
> *In protease inhibitor naive patients, Agenerase is less effective than indinavir.*
>
> *In heavily pretreated protease inhibitor experienced patients, the use of Agenerase has not been sufficiently studied.*

The recommended dosing schedule for Agenerase capsules is 1200 mg twice daily for adults and 20 mg/kg body weight twice daily for children (4 to 12 years) and patients less than 50 kg body weight. The recommended dosing schedule for Agenerase 15 mg/ml oral solution is 17 mg/kg body weight three times daily for children of 4 years and older unable to swallow capsules.

Clinical pharmacology

Pharmacodynamics

- Mechanism of action

Amprenavir is a protease inhibitor with a specific inhibitory activity of the viral protease of HIV-1 and HIV-2. As indicated in Part III, amprenavir has *in vitro* a synergistic effect with zidovudine, didanosine, abacavir and saquinavir. It has also been shown to have an additive effect in combination with indinavir, ritonavir and nelfinavir.

- Resistance profile

The resistance profile has been extensively monitored during the clinical trials. The mutation pattern associated with reduced viral susceptibility to amprenavir appears to be different from those reported with other PIs. Genotypic and phenotypic analyses confirmed that reduced sensitivity of laboratory strains and clinical isolates of HIV-1 to amprenavir is generally mediated via mutation at codon 50 (I50V). When amprenavir was used in an early monotherapy study, the key mutation I50V was associated with high level of resistance.

PI cross-resistance profile following amprenavir failure

In clinical practice (PROAB3006, randomised phase), four principal routes for the development of phenotypic resistance to amprenavir in protease inhibitor-naïve patients have been identified:

- combinations of mutations including the I50V (19% failures)
- or substitutions at position 54 (I54L/M, 21% failures)
- or the I84V substitution (6% failures)
- or the substitutions V32I + I47V (15% failures).

All four routes resulted in cross-resistance with ritonavir, but not with the other available PIs (indinavir, saquinavir and nelfinavir).

Therapy with amprenavir following PI containing regimen failures

Analysis of clinical isolates from 55 PI experienced patients from CNAA2007 revealed at baseline multiple PI mutations which conferred resistance to saquinavir, indinavir, nelfinavir and ritonavir in the range of 72 to 84 %. None of the isolates harboured the I50V mutation, which seemed to confirm that apart from amprenavir none of the PIs select this mutation. Based on phenotypic assays, 30 of these 55 isolates were still sensitive to amprenavir.

Combined analysis of data from published studies, involving PI-experienced patients, indicates that the level of cross-resistance among indinavir, ritonavir and nelfinavir (37-84% of clinical isolates) is considerably higher than observed with amprenavir (18-45%). The incidence of saquinavir resistance was generally lower than for the other PIs except amprenavir.

The potential for cross-resistance between amprenavir and NRTIs and NNRTIs is unlikely considering the different target enzymes involved.

Correlation analyses of the non randomised phase of PROAB3006 (n ~ 40 indinavir experienced patients treated with amprenavir) and PROAB3004 (in children, n = 50) showed that, in addition to baseline viral load, the most important predictor for failure of amprenavir containing therapy in PI experienced patients is the increasing number of key protease inhibitor mutations at baseline. These data are reinforced by the preliminary analysis of the subgroup of patients (n = 111) in whom amprenavir is a component of their antiretroviral salvage regimen (analysis of an ongoing study, NARVAL, aiming to evaluate the use of resistance testing to guide the treatment of PI-experienced patients). Nevertheless, further prospective data are still needed to clarify the predictive value for amprenavir failure of the different combinations of PI mutations, and their relationship with the phenotypic findings.

- Dynamic studies

Preliminary dose escalation studies in adult and children showed that all amprenavir doses tested (150 to 1200 mg) were well tolerated. The most common adverse events reported possibly related to amprenavir were headache and nausea.

Pharmacokinetics

The pharmacokinetic profile of amprenavir has been determined in 15 studies after single and multiple doses ranging from 150 mg single dose to 1200 mg twice a day in healthy volunteers, HIV-1 infected adult patients, children (5 mg/kg to 20 mg/kg dose) and in patients with hepatic impairment. The studies have been conducted using hard capsules and soft capsules containing different amounts of TPGS ranging from 22.9 % to 51 % compared to the formulation intended for marketing. Studies have also been conducted using the oral solution.

Absorption and distribution

After oral administration, amprenavir is rapidly and well absorbed. It has been demonstrated *in vitro* that absorption is mediated by active absorption, amprenavir being a substrate for the counter-transport protein P-glycoprotein (PgP), like other available protease inhibitors.

The absolute bioavailability of amprenavir is unknown due to the lack of an adequate intravenous formulation but has been estimated to be 89% (without taking into account any pre-systemic and first passage metabolism).

Amprenavir exhibits linear pharmacokinetic behaviour, but for single doses up to 1200 mg there are greater than proportional dose related increases in $AUC_{0-\infty}$.

After single administration of doses ranging from 150 to 1200 mg, peak amprenavir plasma concentration is achieved by 2 hours. The oral solution containing 15 mg/ml is more rapidly absorbed with a T_{max} reached in 0.75 hours. A second small peak is observed approximately 10 to 12 hours after the administered dose, which may be due to delayed absorption or enterohepatic circulation.

Following multiple doses ranging from 300 mg bid to 1200 mg bid, the pharmacokinetics is linear at steady-state but no dose proportionality could be observed. Total amprenavir concentrations decreased over the initial 3 to 4 weeks of therapy (48 % at 1200 mg bid). No conclusion can be drawn on the dose proportionality considering the inadequacy of the study design (e.g. limited number of patients, bioinequivalence of the capsules used). Amprenavir has time dependent pharmacokinetics probably due to a reduction in protein binding (lower to alpha-1-acid glycoprotein (AAG) concentration as a result of the antiretroviral therapy). Data do not allow a definitive conclusion on when the steady state total plasma concentrations are reached. At therapeutic dosages (1200 mg twice daily), the mean maximum steady state concentration (C_{maxss}) of amprenavir capsules is 5.36 µg/ml (0.92-9.81) and the minimum steady state concentration (C_{minss}) is 0.28 µg/ml (0.12-0.51). The mean AUC over a dosing interval of 12 hours is 18.46 µg.h/ml (3.02-32.95). No sign of accumulation has been observed. Multiple administration of amprenavir (900 mg, 1050 mg and 1200 mg) in combination with lamivudine and zidovudine, resulted in a large intra-variability reported in amprenavir trough concentrations. Similarly the inter-variability was important for the median trough levels within treatment groups.

Food (standardised high fat breakfast) delayed absorption and decreased both C_{max} (33 and 40 % respectively) and $AUC_{0-\infty}$ (14 and 25 % respectively) in two studies using the clinical trial capsule formulation and the formulation intended for marketing. As the steady state trough concentration ($C_{min,ss}$) was not affected by food intake, amprenavir may be administered with or without food as indicated in the Summary of Product Characteristics.

In vitro, amprenavir is highly protein bound approximately 90 %, mainly to AAG and to a lesser extent albumin. *In vitro* binding of amprenavir to AAG was not linear with the concentration of amprenavir and AAG. The clinical implications are unclear. However, even if a decrease or increase in AAG occurred, there will be no change in the concentration of free substance as long as the unbound (intrinsic) clearance has not changed.

The apparent volume of distribution corrected for the fraction absorbed (V_2/F) decreased with dose and ranged from 336 to 482 l, suggesting that amprenavir penetrates freely into tissue beyond the systemic circulation.

Penetration of amprenavir into cerebrospinal fluid at steady state was poor, with a cerebrospinal spinal fluid to plasma concentration ratio < 1%.

Metabolism and elimination

Amprenavir is primarily metabolised by the liver and less than 3 % excreted unchanged in the urine. As demonstrated during *in vitro* studies, the metabolism is *via* cytochrome P450, mainly CYP 3A4 isoenzyme. Phase I metabolism is essentially oxidative and Phase II metabolism is via UDP-GT and N-acetyl transferase. The main metabolites, inactive *in vitro,* represent 50.3 % of the administered dose .

Clearance of amprenavir following single oral doses ranging from 150 to 1200 mg is estimated to be between 3 and 4.7 ml. The elimination half-life ($t_{½}$) ranged between 7.08 and 9.54 hours. The elimination pathway for amprenavir is mainly through the faeces. Total recovery of a dose of 600 mg was 89 % (range 66-93 %) and approximately 14 % and 75 % was detected as parent drug or metabolites in urine and faeces respectively. Approximately 94 % of the excreted dose in faeces was detected as metabolites.

Special populations

The pharmacokinetic profile of amprenavir has not been established in the elderly and patients with renal dysfunction. Amprenavir is only minimally excreted in urine and therefore the impact of renal impairment should be minimal. Appropriate recommendations have, however, been included in the Summary of Product Characteristics to reflect the lack of data.

In patients with moderate and severe hepatic cirrhosis (Child Pugh score 5-15), $AUC_{0\rightarrow\infty}$ increased significantly compared with healthy volunteers after administration of single oral doses of 600 mg (almost 3-fold in patients with moderate hepatic impairment and 4-fold in patients with severe hepatic impairment). The clinical experience in this patients group is limited but, based on pharmacokinetic data only, the dose recommendations in adults should be reduced as indicated in the Summary of Product Characteristics.

The gender did not seem to influence amprenavir pharmacokinetics, however further data will be collected. Amprenavir exposures were lower in black subjects compared to white which may be linked to differences in AAG levels. The real clinical relevance is currently unknown.

The pharmacokinetic profile of amprenavir in children has been evaluated in single and multiple doses studies. Single dose of amprenavir capsules (5, 10, 15 and 20 mg/kg) was administered to

HIV-1 infected children aged 4 to 12 years. These children had similar pharmacokinetics parameters to those adults ($t_{½}$: 6.2 to 8.3; V_2/F 321 to 360 l). Linear pharmacokinetics in terms of AUC and dose proportionality were observed within this dose-range. The C_{max} of amprenavir increased linearly but less than proportionally. Following multiple doses (15 mg/kg tid oral solution or 20 mg/kg bid oral solution or 20 mg/kg bid capsules) similar exposures to the ones in adults receiving 1200 mg bid were obtained. As the oral solution is 14% less bioavailable than amprenavir capsules, doses of 15 mg/kg tid or 20 mg/kg bid of capsules or 17 mg/kg tid or 22.5 mg/kg bid of oral solution seemed to be sufficient to provide adequate plasma levels.

Interactions studies

Amprenavir is a substrate and a potential inhibitor of CYP3A4. Caution should be exercised when it is co-administered with substrates, inhibitors or inducers of CYP3A4 and relevant information has been included into the Summary of Product Characteristics.

Considering that HIV infected patients are frequently subject to multiple therapies, that amprenavir is extensively metabolised by CYP 3A4, interaction studies have been conducted with commonly co-administered medicinal products. The main findings are displayed in the below tables:

Antiretroviral agents

	Co-administered substances	Population	Dose	C_{max}	AUC	Cmin
Effect on amprenavir pharmacokinetics	***Indinavir***	*Patients*	800 mg tid	↑ 18 %	↑ 33 %	↑ 25 %
	Nelfinavir	*Healthy*	800 mg tid	↓ 14 %	↑ 9 %	↑ 189 %
	Saquinavir	*Healthy*	800 mg tid	↓ 37 %	↓ 32 %	↓ 14 %
	Lamivudine	*Patients*	600 mg (single dose)	↔	↔	N/A
	Zidovudine	*Patients*	600 mg (single dose)	↔	↔	N/A
	Abacavir	*Healthy*	900 mg BID	↑ 47 %	↑ 29 %	↑ 27 %
Effect of amprenavir on the pharmacokinetics of co-administered substance	***Indinavir***	*Patients*	800 mg tid	↓ 22 %	↓ 38 %	↓ 27 %
	Nelfinavir	*Healthy*	800 mg tid	↑ 12 %	↑ 15 %	↑ 14 %
	Saquinavir	*Healthy*	800 mg tid	↑ 21 %	↓19 %	↓ 48 %
	Lamivudine	*Healthy*	600 mg (single dose)	↓16 %	↓ 9 %	N/A
	Zidovudine	*Patients*	600 mg (single dose)	↑ 40 %	↑ 31 %	N/A
	Abacavir	*Patients*	900 mg BID	↔	↔	↔

Based on the results presented in the above table, no dose adjustment is necessary when amprenavir is co-administered with any of these antiretrovirals: indinavir, saquinavir, nelfinavir, lamivudine, zidovudine or abacavir.

A preliminary report indicated that co-administration of amprenavir with efavirenz produced 40 % reductions in AUCss, C_{maxss} and C_{minss} of amprenavir. The magnitude of this interaction seems relevant. The administration of amprenavir and efavirenz without the administration of a pharmacokinetic booster (an appropriate protease inhibitor) is therefore not recommended as it is likely to result in sub-optimal plasma levels of amprenavir. Following Marketing Authorisation, final results of study NIH-IRT 023 were submitted. It concerns a pharmacokinetic sub-study of the interaction between ritonavir, amprenavir and efavirenz in 19 HIV-infected patients with plasma RNA > 500. Patients who had failed therapy with a PI were enrolled into 3 parallel treatment groups: (1) APV 1200 mg BID + RTV 200 mg BID + EFV 600 mg QD (n=6); (2) APV 1200 mg BID + RTV 500 mg BID + EFV 600 mg QD (n=4); (3) APV 1200 mg BID + NFV 1250 mg BID + EFV 600 mg QD (n=9). All patients received abacavir 300 mg BID. The results seem to confirm the lack of effect of efavirenz on amprenavir kinetics when the latter is combined with ritonavir, although the available information is scarce and the number of patients in each group small.

Based on the results of the above study, the CPMP requested the Marketing Authorisation Holder to reword the interaction between amprenavir and efavirenz (variation II/10).

No study has been performed to evaluate the potential interaction between amprenavir and nevirapine, and stavudine. With respect to delavirdine, results from 2 clinical studies were submitted as part of post-approval commitment:

COL10010: A pharmacokinetic study of the interaction between delavirdine and APV in 12 healthy volunteers.

COL30439: A multi-dose pharmacokinetic study of the interaction between delavirdine and APV in 18 healthy volunteers.

Amprenavir (APV) and delavirdine (DLV) are both primarily metabolised by cytochrome P450 3A4 (CYP 3A4). *In vitro* data have shown that delavirdine is a potent inhibitor of CYP 3A4 indicating that delavirdine might inhibit the metabolism of APV. Data from phase I, single dose studies in healthy volunteers have shown that DLV significantly inhibited the metabolism of amprenavir. These studies could not find any significant impact of a single dose of APV on the pharmacokinetic parameters of DLV.

Data from a multiple dose study between APV and DLV in 18 healthy volunteers are available. It was a prospective, open label, randomised, controlled, two-sequence, two-period multiple dose in which

volunteers were randomly assigned to either regimen A (n=9) or regimen B (n=9). Regimen A involved dosing for nine days with amprenavir , 600 mg twice daily, with a 24 hours pharmacokinetic evaluation on day 10 after a single dose of amprenavir 600 mg in the morning. Regimen B involved dosing for nine days with delavirdine, 600 mg twice daily, with a 24 hours pharmacokinetic evaluation on day 10 after a single dose of delavirdine in the morning. Both regimens were followed by regimen C, on day 11, which was amprenavir 600 mg and delavirdine 600 mg twice daily for another nine days with a 24 hours pharmacokinetic evaluation on day 20 after single doses of amprenavir 600 mg and delavirdine 600 mg in the morning. Amprenavir decreased all the delavirdine pharmacokinetic parameters apart from the t_{max}. Particularly, a considerable decrease of 88% in median delavirdine C12h from 7916 to 933 ng/ml was seen. Delavirdine AUC(0-12h) and C_{max} decreased 61% and 47% respectively when co-administered with amprenavir. Delavirdine increased the effect on both the C12h (125%) and AUC(0-12h) (130%) values for amprenavir. The study also showed considerable inter-individual variation in steady-state concentrations of both amprenavir and delavirdine, e.g. an almost 8-fold difference between the lowest and highest C12h value for amprenavir during regimen C, with four of the participants below 252 ng/ml. This means that in a clinical setting some patients could have sub-therapeutic concentrations of both amprenavir and delavirdine

To reflect these data, a revised text for the SPC statement under section 4.5 was proposed, relating to all Agenerase SPCs. (variation II/10).

No data are available with didanosine however it is recommended to administer the two substances one hour apart. Further data on possible interactions will be submitted when available. Preliminary pharmacokinetic data from healthy volunteers showed that amprenavir 450 mg bid co-administered with a low dose of ritonavir resulted in an increased AUC_{ss}, C_{maxss} and C_{minss} by 131 %, 31 % and 680 % respectively. These results suggest that a reduction of amprenavir dose is necessary when used with low dose ritonavir but further data will be submitted to confirm the efficacy and safety of the combination.

The relevant information has been adequately reflected in the Summary of Product Characteristics.

Other medicinal products

	Co-administered substance	**Population**	**Dose**	**C_{max}**	**AUC**	**Cmin**
Effect on amprenavir pharmacokinetics	***Ketoconazole***	Healthy	200 mg bid (single dose)	↓ 16 %	↑ 32 %	N/A
	Clarithromycin	Healthy	1200 mg bid	↑ 15 %	↑ 18 %	↑ 39 %
	Rifampicin		1200 mg bid	↓ 70 %	↓ 82 %	↓ 92 %
	rifabutin	Healthy	1200 mg bid	↓ 7 %	↓ 15 %	↓ 15 %
Effect of amprenavir on the pharmacokinetics of co-administered substance	***Ketoconazole***	Healthy	200 mg bid (single dose)	↑ 19 %	↑ 44 %	N/A
	Clarithromycin	Healthy	1200 mg bid	↓ 10 %	↔	↔
	Rifampicin		1200 mg bid	↔	↔	↔
	rifabutin	Healthy	1200 mg bid	↑ 127 %	↑ 193 %	↑ 349 %

In view of these results, the co-administration of rifampicin with amprenavir is contraindicated.

In addition amprenavir increases rifabutin AUC by 193 % and therefore a reduction of rifabutin dose of at least 50% is recommended when co-administered with amprenavir, although no clinical data is available.

Interaction between amprenavir and methadone has been conducted as part of a follow-up measure, following regulatory approval of Agenerase. Study **COL30330** was a controlled, open-label study to evaluate the pharmacokinetics of amprenavir and methadone enantiomers following co-administration to HIV seronegative, opiate-dependent individuals. The primary objective of this study was to determine the steady-state pharmacokinetics of methadone enantiomers in the presence and absence of

amprenavir. Secondary objectives were to determine the effect of multiple doses of methadone on the steady-state pharmacokinetics of amprenavir, to evaluate the short-term safety of the combination and to correlate methadone dose with the magnitude of amprenavir-induced metabolic inhibition. Nineteen subjects were enrolled. Of these, 16 completed the study. Co-administration of amprenavir and methadone resulted in a 3-4 hour delay in (R-) and (S-) methadone absorption. Plasma (R-) methadone AUCτ,ss was decreased 13% and plasma (R-) methadone Cmax,ss was decreased 25% when methadone was co-administered with amprenavir. Plasma (S-) methadone AUCτ,ss was decreased 40% and plasma (S-) methadone Cmax,ss was decreased 48% when methadone was co-administered with amprenavir.

The 13% reduction in exposure to the active methadone enantiomer was not associated with clinical evidence of methadone withdrawal, findings which indicate no a priori adjustment of methadone is required during co-administration with amprenavir.

With reference to concomitant use of amprenavir and St-John's Wort, serum levels of amprenavir can be reduced by concomitant use of *Hypericum perforatum*. This is due to induction of drug metabolising enzymes by *Hypericum perforatum*. Herbal preparations containing *Hypericum perforatum* should therefore not be combined with Agenerase. If a patient is already taking *Hypericum perforatum*, amprenavir and if possible viral levels should be checked and *Hypericum perforatum* stopped. Amprenavir levels may increase on stopping *Hypericum perforatum* preparations.

The Marketing Authorisation Holder conducted a study **(PRO10018)** to evaluate the interaction between amprenavir and a combination of an oral contraceptive Ortho-Novum 1/35 (0.035 mg ethinyl estradiol plus 1.0 mg norethindrone). The primary objectives of the study were: to determine the effects of co-administration of amprenavir with Ortho-Novum 1/35 on the pharmacokinetic of amprenavir, ethinyl estradiol and norethindrone, to evaluate the tolerability of Ortho-Novum when co-administered with APV, as well as to determine if any dosage adjustment is appropriate for either drug due to their concomitant administration. The secondary objective was to determine what, if any, effects there were of APV co-administration on FSH and LH.

Twenty-five healthy female subjects were enrolled into the study and began treatment with OC. All these were included in the safety analysis but only ten provided data for the pharmacokinetic and pharmacodynamic analyses.

Regarding the pharmacokinetic parameters, oral contraceptive co-therapy with APV resulted in a decrease of 22% (90% CI: 0.65-0.92) in serum APV AUCτ,ss. The 9% decrease (90% CI: 0.80-1.03) in APV Cmax,ss was within the pre-specified range of 0.7-1.43. As a result, it is concluded that the concomitant use of Agenerase and contraceptive pill may result in a decrease of the therapeutic effect of Agenerase. Consequently, the Marketing Authorisation Holder has reworded section 4.4 (Special warnings and special precautions for use) and 4.5 (Interactions with other medicinal products and other forms of interactions) of the SPC in order to recommend the use of an alternative method of contraception instead of "additional" ones.

Bioequivalence studies

The bioequivalence between the different formulations used during the clinical trials has been investigated. Bioequivalence was demonstrated in terms of AUC but not C_{max} between the hard capsule (150 mg) and soft capsule (150 mg) formulations. The two different strengths of the proposed marketed formulations 50 and 150 mg soft capsules are bioequivalent for AUC and C_{max} and can therefore be interchanged.

The comparative rate and extent of absorption between different formulations of amprenavir have been evaluated in 4 single dose (600 mg) randomised open label, cross over studies. The oral solution has a lower bioavailability compared with the 50 and 150 mg soft capsules. AUC and C_{max} were 14% (CI 90%: 4% to 23%) and 19 % (CI 90 %: 7 % to 29 %) lower at equivalent doses than the 150 mg soft capsules formulation intending for marketing. Therefore an adequate statement has been introduced in the Summary of Product Characteristics to highlight that equal doses of the soft capsules and the oral solution are not bioequivalent and therefore can not be interchangeable on a milligram per milligram basis.

Clinical efficacy

In adults, two dose ranging studies and two phase III studies, in antiretroviral naive patients and antiretroviral experienced but protease inhibitor naive patients, have been conducted. In the paediatric population, amprenavir was evaluated in one phase II study and one phase III study. Five supportive studies in adults have also been submitted. The efficacy of amprenavir was evaluated in a total of 1215 adults and 268 paediatric patients.

Dose response studies and main clinical studies

Dose response studies

Pharmacokinetic data do not fully justify the recommended 1200 mg bid dose. Mean total concentrations of amprenavir 12 hours after the 1200 mg single dose were greater than the *in vitro* IC50 for HIV-1 IIIB (0.04 μg/ml). However, **for some patients**, unbound plasma concentrations 12 h after single dose are below this value.

Two dose response, open label, studies have been performed in protease inhibitor naive adult patients and the pharmacokinetic/pharmacodynamic relationship was evaluated.

The first non-randomised study **PROA1002** included three distinct phases. In the first phase, the antiviral activity was evaluated over 4 weeks of multiple doses of amprenavir monotherapy (300 mg, 900 mg, 1050 mg and 1200 mg twice daily). A cohort with 900 mg bid amprenavir treatment, in combination with abacavir, was also included. Baseline characteristics differed between cohorts, median HIV-1 RNA levels ranged from 4.91 $\log_{10}$ copies/ml in the amprenavir 1200 mg group to 4.29 $\log_{10}$ copies/ml in the amprenavir 1050 mg group. The relationship between amprenavir concentrations and the decrease in the time-weighted average AUC minus the baseline (AAUCMB) in HIV RNA over 4 four weeks was assessed. It was estimated that the C_{minss} of total amprenavir in plasma to provide 90% of the maximum decrease in AAUCMB over 4 weeks is 0.23 μg/ml [EC_{90}]. The C_{minss} medians for amprenavir after 1050 and 1200 mg bid doses were 0.29 and 0.28 μg/ml respectively which therefore exceeded the EC90. No difference could be seen between the doses, however the design of the study (baseline characteristics not well balanced, non randomised and small size) did not allow definitive conclusions. These three dose levels were, however, evaluated in combination therapy with NRTIs in the subsequent study PROA2002 over a longer period of time.

This study **PROA2002** included three doses of amprenavir (900, 1050 and 1200 mg bid) and placebo in combination with lamivudine and zidovudine in 80 lamivudine and protease naive patients (CD4 cell counts > 150 cells/mm^3 and plasma HIV-1 RNA levels > 10,000 copies/ml).

At week 12, the four treatment arms were compared with respect to AAUCMB for HIV-1 RNA and CD4 cell counts. Results are displayed in the table below:

HIV-1 RNA and CD4 cell counts changes at week 12

	Placebo + LAM/ZDV (n = 20)	**APV 900 mg + LAM/ZDV (n = 21)**	**APV 1050 mg + LAM/ZDV (n = 22)**	**APV 1200 mg + LAM/ZDV (n = 21)**
HIV-1 RNA ($\log_{10}$ copies/ml)				
Baseline [1]	4.65	5.14	4.78	4.96
Week 12 [2]	-1.47	-1.41	-1.70	-1.76
CD4 cell counts (cells/mm^3)				
Baseline[1]	422	405	312	401
Week 12 [2]	+ 52	+ 113	+ 79	+ 55

[1] median; [2] median AAUCMB while on trial medication; LAM = lamivudine; ZDV = zidovudine; APV = amprenavir

There were no statistically significant differences either between any of the three treatment groups and the placebo group nor between the three treatment groups.

After week 12, all patients of the placebo arm received amprenavir 1050 mg bid and the study was continued to collect data on the durability of the antiviral effect of amprenavir in combination with lamivudine and zidovudine as detailed below:

Proportion of patients with plasma HIV-RNA values < 400 copies/ml at week 12 and week 60 (Intent-to-treat or ITT, Per protocol or PP populations)

	Placebo	APV 900 mg (n = 21)	APV 1050 mg (n = 22)	APV 1200 mg (n = 21)
Baseline HIV-1 RNA log_{10} copies/ml (range)	4.65 (3.35 – 5.21)	5.14 (3.34 – 5.98)	4.78 (3.81 – 6.15)	4.96 (2.51 – 5.82)
Week 12				
ITT		43 % (9/21)	59 % (13/22)	29 % (6/21)
PP		60 % (9/15)	70 % (14/20)	62 % (8/13)
Week 60				
ITT		25 % (5/20)	43 % (9/21)	20 % (4/20)
PP		64 % (7/11)	79 % (11/14)	86 % (6/7)

There was no statistical difference between the two dosage regimens (1200 mg and 1050 mg bid) however the study was not powered to demonstrate any difference between the doses.

On the basis of data from studies PROA1002 and PROA2002, no difference could be found between the doses 1200 mg bid and 1050 mg bid regarding either their pharmacokinetic profile or antiviral activity. Furthermore, in one of the supportive studies, PROA2001, amprenavir 800 mg tid resulted in comparable C_{minss}, inducing a viral load reduction similar to that observed with 1050 mg bid in study PROA2002. It cannot, therefore, be ruled out that the three time daily dosing schedule could result in equal efficacy and better safety. Doses of amprenavir higher than 1200 mg bid or 800 mg tid have not been evaluated.

In conclusion, the proposed dosage recommendation proposed by the applicant, 1200 mg bid, was questioned and was further addressed during the hearing. Although the twice daily regimen is not fully justified to exclude any risk that C_{minss} may fall below antiretroviral levels compared to the three times daily regimen, 1200 mg bid has been used in the main studies.

Main studies

Results up to 24 weeks from two main studies in adult patients using 1200 mg twice daily as dosage regimen were initially provided in the submission of the application. The efficacy and safety of amprenavir has been evaluated in antiretroviral naive and experienced patients. Amprenavir in triple combination with NRTIs has been compared to placebo (PROAB3001) and to indinavir (PROAB3006). The initial documentation has been supplemented by results through 48 weeks.

The efficacy and safety of amprenavir in combination with NRTIs have also been evaluated through 24 weeks in paediatric patients over the age of 4 years.

The overview of the main clinical studies in adults and children is displayed in the table below:

	PROAB3001	PROAB3006	Paediatric study PROB2004	Paediatric study PROAB3004
Period reported	48 weeks	48 weeks		
Study design	Randomised Multicentre Double blind Placebo controlled	Randomised Open label Active comparator controlled	Randomised Multicentre Open label Active comparator controlled	Randomised Multicentre Double blind Placebo controlled
Initial study drug arm	APV/LAM/ZDV Placebo/LAM/ZDV APV: 1200 mg bid LAM: 150 mg bid ZDV: 300 mg bid	APV/NRTIs IDV/NRTIs APV: 1200 mg bid IDV: 800 mg tid	20 mg/kg bid APV/NRTIs 15 mg/kg tid APV/NRTIs	Randomised 1200 mg or 20 mg/kg bid APV/2 NRTIs Placebo/2NRTIs amendment Open label 1200 mg or 20-22.5 mg/kg bd amprenavir/NRTIs

Amprenavir formulation	200 mg soft capsules 150 mg soft capsules	150 mg soft capsules	15 mg/ml oral solution 50 mg/150 mg soft capsules	15 mg/ml oral solution 50 mg/150 mg soft capsules
Inclusion criteria	Adult Protease naive 4 weeks NRTI or NNRTI CD4 ≥ 200 cells/mm^3 HIV-1 RNA ≥ 10,000 copies/ml	Adult NRTI experienced Protease naive 12 weeks prior lifetime NRTI treatment HIV RNA ≥400 copies/ml	Paediatric > 2 years and less than 13 years PI naive or experienced HIV RNA > 400 copies/ml	Subjects ≤ 18 years able to swallow capsules PI naive HIV-1 RNA≥10,000 copies/ml Amendment Open label Non comparative Paediatrics 4 years to 18 years PI naive/experienced HIV-1 RNA≥ 400 copies/ml
Patients initiating study medication	N = 102 N = 112 (control arm)	N = 245 N = 241 (control arm)	N = 40	N = 229

APV: amprenavir; LAM = lamivudine; ZDV = zidovudine

Study PROAB3001: antiretroviral naive adult patients

The study was planned to enrol 290 patients. However due to changes in the clinical management of HIV infected patients, the sample size was reduced to 230 patients. A total of 232 patients over 18 years of age were therefore randomised, 116 in each group.

Patients were to continue their randomised therapy until all patients completed 48 weeks unless they met a protocol defined switch criterion defined as two consecutive plasma HIV-1 RNA ≥ 400 copies/ml at week 16 or thereafter or progression to CDC class C event or experienced a treatment limiting adverse event.

The primary endpoint was the proportion of patients with plasma HIV-1 RNA plasma levels below 400 copies/ml as measured by PCR assay without progression to a new AIDS-defining condition or permanent discontinuation of randomised therapy. The primary analysis was the intent-to-treat (ITT) analysis (i.e. missing patients were regarded as failures and all premature discontinutions of randomised therapy, all new confirmed CDC Class C events, and deaths, carried forward as treatment failures). The response was also analysed in the per protocol population (i.e. data collected during randomised therapy only).

Results

Population

The demographic and baseline characteristics were very similar in each treatment group.

	By treatment group	
	PLO + LAM/ZDV	APV + LAM/ZDV
N	116	116
Median (range) baseline HIV-1 RNA log $_{10}$ copies/ml	4.74 (3.06 – 6.31)	4.64 (3.61 – 6.09)
Median (range) baseline CD4 cell counts (cells/mm^3)	410 (139 –984)	442 (216 –1800)

PLA = placebo; LAM = lamivudine; ZDV = zidovudine; APV = amprenavir

Approximately 80 % of the patients were asymptomatic. The median age was 35 years old and 89 % were male. The percentage of patients who completed 48 weeks of treatment with the randomised therapy was 12 % in the placebo group and 48 % in the amprenavir group. Of more patients who stopped treatment prior to week 48 most met switch criteria (placebo arm: 81 %; amprenavir arm: 24 %) or experienced adverse events (5 % versus 31 % in the placebo and amprenavir groups respectively).

Plasma HIV-1 RNA levels

The proportion of patients with plasma HIV-1 RNA plasma levels below 400 copies/ml at week 48 is displayed in the below table:

	Number of patients with HIV-1 RNA levels < 400 copies/ml per treatment group at week 48 (n/N, %)					
	ITT: missing = failure		ITT: data as collected *		PP	
	PLO + LAM/ZDV N = 116	APV + LAM/ZDV N = 116	PLO + LAM/ZDV N = 116	APV + LAM/ZDV N = 116	PLO + LAM/ZDV N = 107	APV + LAM/ZDV N = 109
By HIV-1 RNA strata 10,000 – 30,000 > 30,000 – 100,000 > 100,000	 3/37 (8 %) 1/55 (2 %) 0/24 (0 %)	 19/37 (51 %) 23/55 (42 %) 6/24 (25 %)	 15/24 (63%) 26/33 (79%) 13/17 (76%)	 21/27 (78 %) 28/31 (90 %) 8/13 (62%)	 4/10 (40%) 1 /2 (50%) 0/0	 20/23 (87 %) 24/24 (100 %) 6/7 (86%)
Total population	4/116 (3 %)	48/116 (41 %)	54/74 (73%)	57/71 (80 %)	5/12 (42%)	50/54 (93 %)

ITT = intent-to-treat; PP = per protocol

* all data as collected analysed until the last study related visit regardless of whether patients were still receiving the original randomised therapy.

	PLO + LAM/ZDV		APV + LAM/ZDV	
	< 400 copies/ml	< 50 copies/ml	< 400 copies/ml	< 50 copies/ml
Total population at 16 week	17/116 (15 %)	10/116 (9 %)	64/116 (55 %)	51/116 (44 %)
Total population at 48 week	4/116 (3 %)	1/116 (1 %)	48/116 (41 %)	40/116 (34 %)

In conclusion, the triple therapy with amprenavir plus lamivudine/zidovudine in antiretroviral naive patients was superior to dual therapy with these nucleoside analogues ($p < 0.001$). The durability of the response with the triple therapy regimen up to 48 weeks should however be interpreted with caution in view of an apparent decline in the response after week 16.

Study PROAB3006 antiretroviral experienced adult patients

This study was designed as an open label non inferiority trial to compare the efficacy and safety of amprenavir versus indinavir, when administered in combination with unspecified NRTI therapy in NRTI experienced and PI naïve HIV infected patients. The open label design was chosen in view of the practical problems with blinding the differences in daily pattern of study drug administration (twice daily for amprenavir versus three times daily for indinavir) and the need to increase fluid intake with indinavir.

The primary endpoint was the number of patients with HIV-1 RNA plasma levels below the limit of detection (400 copies/ml). The primary population for the efficacy analysis was the ITT population although a PP analysis was also performed. Two ITT analyses were performed: 'ITT: missing = failure', in which all missing values were considered failures, and subjects permanently discontinuing randomised treatment and experiencing CDC class C events were carried forward as failures; and, 'ITT: data as collected' in which all data were included, regardless of whether patients were still receiving the original randomised or assigned therapy, without any imputation for missing values.

A total of 504 subjects were enrolled in this study and subsequently randomised to amprenavir (n = 254) and to indinavir (n = 250). The study was powered, at least 80 %, to show non-inferiority in the success rates between the treatment groups over 48 weeks of therapy, using 95 % confidence intervals. Results at 48 weeks have been provided.

Results

Population

Baseline demographic and characteristics were similar between the treatment groups. The majority of the patients were asymptomatic.

	By treatment group	
	Amprenavir + NRTIs	Indinavir + NRTIs
N	254	250
Median baseline HIV-1 RNA $\log_{10}$ copies/ml	3.87	3.98
Median baseline CD4 cell counts	389	414

To mimic the current therapeutic management of the patients, randomisation was stratified according to the investigator's intention, at screening, to change at least 1 NRTI in the patient's treatment regimen at day 1. The treatment groups were similar with respect to background treatment. The majority of patients received lamivudine or stavudine.

The percentage of patients who discontinued the study prior to week 16 was higher in the amprenavir arm (30 %) than in the indinavir arm (15 %). The results at 48 weeks showed, however, that the overall rate of discontinuation of treatment due to adverse events was similar in both treatment arms.

Plasma HIV-1 RNA levels at 48 weeks

	Number of patients with HIV-1 RNA levels < 400 copies/ml per treatment group at week 48 (n/N, %)					
	ITT: missing = failure		ITT: data as collected		PP	
	APV/NRTIs N = 254	IDV/NRTIs N = 250	APV/NRTIs N = 254	IDV/NRTIs N = 250	APV/NRTIs = 236	IDV/NRTIs N = 237
By HIV-1 RNA strata ≥ 400 – 10,000 > 10,000 – 100,000 > 100,000	 52/140 (37%) 19/94 (20%) 6/20 (30%)	 72/137 (53%) 40/93 (43%) 3/20 (15%)	 65/100 (65%) 25/54 (46%) 8/11 (73%)	 82/105 (78%) 51/70 (73%) 5/11 (45%)	 53/79 (67%) 19/35 (54%) 6/8 (75%)	 74/91 (81%) 39/51 (76%) 4/6 (67%)
Total population	77/254 (30 %)	115/250 (46%)	98/165 (59%)	138/186 (74%)	78/122 (64%)	117/148 (79%)

APV = amprenavir; IND = indinavir

The proportion of patients with HIV-1 RNA < 400 copies/ml and 50 copies/ml at 16 and 48 weeks, in the ITT population analysis (with missing values imputed as failures and premature discontinuations of randomised treatment and clinical progressions carried forward as treatment failures) are displayed in the table below:

	APV/NRTIs		IDV/NRTIs	
	< 400 copies/ml	< 50 copies/ml	< 400 copies/ml	< 50 copies/ml
Total population at 16 week	113/254 (40 %)	89/254 (35%)	147/250 (59 %)	117/250 (47%)
Total population at 48 week	77/254 (30%)	58/254 (23 %)	115/250 (46 %)	93/250 (37 %)

Results seemingly revealed a superiority of the indinavir containing regimen. In the ITT population, median increases from baseline in CD4 cell counts was measured as a secondary endpoint and accounted for 27 cells/mm^3 in the amprenavir group and 44 cells/mm^3 in the indinavir group at week 16.

The combination therapy with amprenavir and NRTIs in antiretroviral experienced patients seemed therefore less efficacious in reducing viral load below the limit of detection of the two assays used (400 copies/ml and 50 copies/ml). The final report will be provided when available.

Supportive studies

Monotherapy

Study **ACTG 347** compared amprenavir alone with amprenavir in combination with lamivudine and zidovudine in antiretroviral naive and experienced HIV-1 infected patients (plasma HIV-1 RNA levels of at least 5,000 copies/ml). This study was terminated early following an interim review. The final analysis showed similar plasma HIV-1 RNA reductions at week 2 in both arms but rebound of the viral load in the monotherapy arm led to a median decline in plasma HIV-1 RNA of only 0.91 $\log_{10}$ copies/ml at week 12 compared to more than 2.16 $\log_{10}$ copies/ml in the triple therapy arm. Monotherapy with amprenavir is not recommended as stated in the Summary of Product Characteristics.

Double therapy

An open label, randomised study, **PROA2001**, investigated amprenavir (800 mg tid) in dual therapy with different protease inhibitors (saquinavir soft capsules, indinavir and nelfinavir) in the absence of NRTIs therapy in protease naive patients. At week 3, lamivudine plus zidovudine were added to the amprenavir monotherapy group. Median reductions from baseline of approximately 2 $\log_{10}$ copies/ml or greater were observed in the saquinavir and indinavir combination treatment groups from week 4 through 24. Although these values were slightly lower in the nelfinavir/amprenavir and amprenavir/lamivudine/zidovudine groups, no conclusion regarding efficacy differences could be drawn in view of the small sample size (n=33).

Study **CNAA2004** was an open label randomised study designed to evaluate abacavir in dual therapy with different protease inhibitors including amprenavir, saquinavir, indinavir, ritonavir and nelfinavir. The study included a small number of patients (82 patients randomised). The data at 48 weeks did not demonstrate equivalence or a difference between the different PI containing regimens, but the study was not powered to do so. In the PP analysis, amprenavir/abacavir seemed to be as effective as indinavir/abacavir (90 %) although ritonavir/abacavir (100 %) appeared more effective. Due to the reduced sample size in each treatment arm, these results should be taken with caution.

Quadruple therapy

Study PROA2003, an open label and non randomised study was designed to evaluate the efficacy and safety of amprenavir in combination with abacavir, zidovudine and lamivudine. Patients were either chronically infected with HIV (protease inhibitor and lamivudine naive patients) or were acutely infected with HIV (antiretroviral naive patients). Of twenty four patients initially enrolled into the study, 20 completed 24 weeks. The majority of the patients had less than 30,000 copies/ml at baseline. In the ITT population (failures carried forward) the majority of patients had plasma levels below the limit of detection of the assay used (< 500 copies/ml) at week 24 (10/13, 77 % of the acutely infected patients and 7/11, 64 % of the chronically infected patients). The interpretation of the contribution of amprenavir to the therapeutic effect is limited by the design of the study, the low baseline plasma HIV-1 RNA levels and limit of detection of the assay used.

Efficacy in children

The efficacy of amprenavir has been evaluated in two ongoing paediatric studies using amprenavir as oral solution, which represents an adequate formulation for paediatric purposes, in combination with NRTIs. Results of both studies involving a total of 268 HIV infected children who have received amprenavir oral solution or capsules with NRTI therapy for an average duration of 4 months. One hundred and fifty three children were exposed to amprenavir for at least 12 weeks and 61 for more than 6 months. Both studies included naïve and experienced PI children.

Based on the results from the pharmacokinetics analysis evaluated in PROA1006 and PROB2004 the exposure after administration of doses of 15 mg/kg tid or 20 mg/kg bid are in the same range as those in adult patients.

In the open label study **PROB2004**, the efficacy and safety of amprenavir oral solution (15 mg/ml) in combination with NRTIs in HIV-infected patients below 13 years old (plasma HIV-1 RNA levels > 400 copies/ml). Patients were enrolled sequentially according to age (7 years to 13 years, 4 years to 7 years and 2 to 4 years) and were randomised to receive amprenavir 20 mg/kg bid or amprenavir 15 mg/kg tid.

The study **PROAB3004,** was initially carried out to evaluate amprenavir against placebo in combination with NRTIs in children aged from 6 months to 18 years. The protocol of the study was amended following the availability of guidelines recommending more aggressive treatment in paediatric population to an open label non comparative phase III study. This amendment coincides with the availability of the oral solution.

Patients ≥ 13 years of age with weight ≥ 50 kg received 1200 mg BID as 50 or 150 mg capsules. Patients less than 13 years old or patients with weight less than 50 kg received the dose of 20 mg/kg bid in the form of 50 mg capsules. Children unable to swallow capsules received amprenavir oral solution at the dose of 22.5 mg/kg bid, adjusting for the lower bioavailability of the oral solution. The most frequent NRTI combinations at study entry for both PI naïve and experienced patients were stavudine/ddI (27 %), lamivudine/stavudine (23 %) and lamivudine/zidovudine (21 %).

The primary efficacy endpoint is the proportion of patients who reached plasma HIV-1 RNA below 400 copies/ml at week 48, ITT population analysis of all collected data. A PP analysis of data collected until study discontinuation (with data censored post deviation or dose adjustment) has also been performed. Preliminary results at week 16 and 24 are displayed in the table below:

	PROB2004				PROAB3004			
	PI naïve N= 25		PI experienced N = 15		PI naïve N= 109		PI experienced N = 120[b]	
	Week 16	Week 24	Week 16	Week 24	Week 16	Week 24	Week 16	Week 24
N – ITT	16	13	5	6	53	34	53	15
N - PP	9	9	2	2	48	30	46	11
Patients with < 400 copies/ml HIV RNA (n, %)								
ITT[1]	10 (63%)	6 (46%)	0	0	19 (36%)	11 (32%)	7 (13%)	2 (13%)
PP[2]	6 (67%)	4 (44%)	0	0	18 (38%)	11 (37%)	5 (11%)	2 (18%)
Median change from baseline in HIV-1 RNA log10 copies/ml								
ITT[1]	- 1.8	- 1.0	- 0.3	- 1.0	- 1.0	- 0.9	- 0.4	- 0.4
PP[2]	- 1.9	- 1.8	- 1.4	- 0.8	- 1.1	- 1.0	- 0.3	- 0.3
Median change from baseline in CD4 cell counts/mm^3								
ITT[1]	62	134	61	51	81	130	69	5
PP[2]	153	158	82[a]	- 46	81	120	51	- 40

[1] Intent to treat of all collected data
[2] Per protocol analysis of data collected until study drug discontinuation with data censored post deviation or dose adjustment
[a] only 2 patients provided data
[b] includes one patient not exposed to amprenavir

Only 5 % of patients in both studies discontinued because of adverse events related to gastro-intestinal tract and rash.

Efficacy results are strongly influenced by the previous therapy with the PI naive patients showing the best response to treatment. The changes in CD4 cell counts are consistent with the pattern observed for the virological response.

The tid regimen of amprenavir oral solution used in study PROB2004 seems more effective than the bid at week 24 (25 % of the patients in the bid regimen reached plasma HIV RNA less than 400 copies/ml versus 43 % in the tid regimen), however the baseline characteristics and concomitant antiretroviral therapy were not the same in the two groups.

Sufficient data have been provided in terms of number of patients exposed and duration. Altogether and despite the small numbers precluding statistical comparison, a three times daily dosage regimen with the oral solution is supported by a better tolerability, less variability in plasma concentrations and a higher probability to achieve effective plasma concentrations.

Final reports on the two paediatric studies, PROB2004 and PROAB3004 confirm that amprenavir is an effective antiretroviral agent in children.However, considering the scarcity of the data in children aged 2-<4 years (i.e. 17 patients, 6 % of the paediatric population), amprenavir is not indicated in this age range.

Amprenavir treatment in PI experienced patients

Study **CNAA2007** was designed as an open label study to evaluate the efficacy and safety of amprenavir in combination with abacavir and efavirenz in HIV-1 infected patients with HIV-RNA ≥ 500 copies/ml despite previous treatment with at least one of the following PIs: indinavir, ritonavir, saquinavir and/or nelfinavir. Patients were to be treated for 48 weeks. Overall 25 % and 23 % of the patients included in the ITT population (missing = failure) analysis (n = 101) had plasma HIV-1 RNA below 400 copies/ml at weeks 16 and 48 respectively. Analysis per stratum showed that patients with pre-entry viral load < 40,000 copies/ml and no prior NNRTI experience were more likely to achieve an endpoint of plasma HIV RNA below 400 copies/ml (53 % response rate) than were patients in any other stratum subgroup/NNRTI experienced (range 7 –33%) (ITT collected data only). The interaction between amprenavir and efavirenz which resulted in approximately 40 % reduction in amprenavir plasma concentrations, indicates that amprenavir had not been optimally dosed in this study. No dose adjustment of amprenavir had been made to take account of the interaction. Hence the quantitative contribution of amprenavir to the therapeutic effect cannot be assessed. The results of this study do not provide any clear evidence of the efficacy of amprenavir as salvage therapy.

Considering the potential interest of amprenavir as a second line PI therapy based on the *in vitro* resistance profile, the CPMP requested the applicant to provide further data on the response of PI-experienced patients to subsequent amprenavir containing regimen and vice-versa to substantiate the benefit of amprenavir in this indication.

Results from ongoing studies ACTG 398, PROAB3006 (open label extension phase), ICC-605, CNAF3011 and PROAB3004, where PI experienced adults and children changed to an amprenavir containing regimen, were therefore submitted. Data on amprenavir-experienced adult patients who changed to a different PI-containing regimen were also provided.

An overview of studies ACTG 398, ICC-605 and CNAF3011 is summarised below

Study	Design	Inclusion criteria	Population	Duration	Regimen
ACTG398 US	Phase II, randomised, ongoing	prior exposure to up to 3 PIs plasma HIV RNA ≥ 1,000c/ml naïve to study quad regimen	460	48 weeks	APV/ABC/EFV/ADV vs same quad +SQV vs same quad + IDV vs same quad + NFV
ICC-605 sub-protocol to ICC-006 US	Phase II, open label pilot non controlled study	prior exposure to PIs naïve to NNRTIs naïve to study regimen plasma HIV RNA ≥ 2000c/ml	25	24 weeks	APV/ABC/EFV/ADV
CNAF3011 France	Phase II, open label pilot non controlled study	experienced with ≥ 1 PI naïve to ABC, APV, HU CD4 > 100c/mm^3 plasma HIV RNA > 10,000 c/ml	20	48 weeks	ABC/APV/ddl/HU

APV = amprenavir; ABC = abacavir; EFV = efavirenz; ADV = adefovir; ddI = didanosine SQV = saquinavir; IDV = indinavir; NFV = nelfinavir; HU = hydroxyurea

A summary of the results on the antiviral response of PI-experienced patients to an amprenavir-containing salvage regimen is presented in the table below:

Study	Regimen	Baseline HIV-1 RNA log 10 copies/ml	Patients with < limit of detection[1] copies/ml HIV-1 RNA at week 24			
			As treated or missing excluded		ITT: Missing = failure	
			NNRTI naive	NNRTI experienced	NNRTI naive	NNRTI experienced
ACTG398	APV/PI/ NRTI/NNRTI APV/NRTI/NNRTI	4.7 4.7	72 % (69/96) 53 % (30/57)	38 % (27/71) 12 % (3/25)	47 % (84/147) 33 % (31/93)	19 % (28/147) 8 % (5/64)
ICC-605	APV/ NRTI/NNRTI NRTI/NNRTI	4.6	62 % (8/13)	-	32 % (8/25)	-
PROAB3006	APV/NRTIs	2.8	63 % (10/16)			
CNAA2007	APV/ABC/EFV	5.1	54 % (15/28)	26 % (5/19)	30 % (18/60)	12 % (5/41)

1. LOD – Assay Limit of Detection for ACTG398 = 200c/ml, PROAB3006 and CNAA2007 = 400c/ml, ICC-605 = 500c/ml
2. After Week 24 in this study subjects were able to modify their treatment regimen to increase the APV exposure by adding ritonavir (RTV) at a dose of 100mg BID and reducing the dose of APV to 600mg BID. Ten of the twenty subjects introduced low dose RTV after Week 24, achieving an additional median 1.15 $\log_{10}$ copies/ml reduction in plasma HIV-1 RNA 4 weeks later, indicating the potential value of this combination.
3. Sensitivity to ABC and APV was therefore an important predictor of treatment response.

Based on these results, amprenavir seemed to contribute to the antiviral effect of combination regimens in PI experienced patients. Nevertheless, the design of the studies had some limitations, which do not allow drawing definite conclusions on the specific role of amprenavir in such therapy regimen. For instance, in ACTG 398, there was no arm without amprenavir. In addition, the proportion of patients previously exposed to at least 3 PIs varied greatly among groups which makes it difficult to compare different dual PI based therapies (from 26 % for the amprenavir/saquinavir arm to 80 % for amprenavir/nelfinavir).

Complex pharmacokinetics drug interactions added to the difficulty in assessing the true contribution of amprenavir to the salvage regimens and the comparison among treatment arms.

There is only limited and non controlled information on the value of amprenavir as rescue therapy in PI experienced children.

However from the data, the value of amprenavir in PI experienced patients seems to be conditioned by the number of new drugs that are introduced in the rescue regimen, the extent of the previous exposure to other PIs and the presence of key PI mutations at baseline.

In addition, some data on PI therapy for amprenavir experienced patients who participated in the open label extension of PROAB3006 or ACTG373 (an open label extension of ACTG347) were provided. Data from ACTG 373, in which almost half of the patients had been previously treated with amprenavir monotherapy showed that the quadruple therapy indinavir/nevirapine/stavudine and lamivudine achieved a high response rate, maintaining plasma HIV-RNA < 500 copies/ml in approximately 60 % of patients over 48 weeks.

Clinical safety

The safety database for amprenavir consists of data collected from the different clinical trials where over 1,000 patients have been exposed to amprenavir. The safety profile is mainly based on the two main studies PROAB3001 and PROAB3006 where results have been provided through 48 weeks and patients have been exposed to amprenavir for a median duration of 249 days and 391 days respectively.

The most frequent adverse events clinical adverse events (AEs) [≥ 10% in any treatment arm, of any severity (Grade 1 to 4) and regardless of the investigator's assessment of causality], reported during the randomised phase of PROAB3001 and PROAB3006, respectively are displayed in the table below:

	PROAB3001		**PROAB3006**	
	Placebo + LAM/ZDV	**Amprenavir + LAM/ZDV**	**Indinavir + NRTIs**	**Amprenavir + NRTIs**
Prior antiretroviral therapy	no	no	yes	yes
No subjects exposed	109	113	241	245
Median (range) duration of exposure in days	146 (1-561)	249 (2-595)	396 (6-526)	391 (1-531)
% subjects with at least one adverse event	94%	100%	95%	96%
Most frequent AEs (No subjects, %)				
Nausea	55 (50)	84 (74) [b]	85 (35)	106 (43)
Fatigue	40 (37)	42 (37)	64 (27)	42 (17)
Vomiting	19 (17)	38 (34)	48 (20)	58 (24)
Gaseous symptoms	48 (44)	37 (33)	26 (11)	43 (18)
Diarrhoea	27 (25)	35 (31)	89 (37)	130 (53) [b]
Headache	31 (28)	33 (29)	64 (27)	63 (26)
Rash	7 (6)	31 (27) [b]	36 (15)	49 (20)
Oral/perioral paresthesia	7 (6)	29 (26) [b]	6 (2)	76 (31) [b]
Viral respiratory infections	15 (14)	28 (25)	55 (22)	67 (28)
Sinus disorders	11 (10)	18 (16)	30 (12)	31 (13)
Loose stools	16 (15)	13 (12)	20 (8)	42 (17)
Abdominal discomfort	15 (14)	14 (12)	20 (8)	20 (8)
Fever	7 (6)	14 (12)	7 (6)	14 (12)
Ear nose and throat infections	9 (8)	14 (12)	70 (29)	50 (20)
Cough	13 (12)	12 (11)	44 (18)	29 (12)

[b]: Fisher's exact test: $p < 0.001$

Most patients experienced only Grade 1 or moderate events.

A subgroup analysis, according to the most frequent combination therapies used in PROAB3006 confirms that rash and oral paresthesia are related to amprenavir as the incidence was similar in all subgroups.

The incidence of nausea and vomiting in patients treated with amprenavir was lower in study PROAB3006 compared to PROAB3001. The subgroup of patients treated with amprenavir in combination with lamivudine/zidovudine showed an incidence of nausea and vomiting similar to that of the overall population of PROAB3006. Diarrhoea is one of the most reported adverse events with amprenavir (14 %). The incidence of diarrhoea was 63 % and 60 % in subgroups receiving amprenavir in combination with ddI or stavudine as compared to 53 % in the overall population treated with amprenavir during the randomised phase of study PROAB3006. These results confirmed that stavudine or ddI play an important role in the overall high incidence of diarrhoea in this study. Diarrhoea appeared to have no impact on the plasma concentration of APV and antiviral response.

The relative safety profile of amprenavir and indinavir was compared over a median duration of exposure for each substance of 56 weeks. Globally the nature of the clinical adverse events was similar between amprenavir and indinavir arms. The overall proportion of patients reporting any clinical adverse events was similar in each treatment group (96 % in amprenavir arm versus 95 % in indinavir arm) but was lower for amprenavir with respect to laboratory abnormalities of any grade (85 % in amprenavir arm versus 95 % in indinavir arm). The frequency however was different for diarrhoea and oral/perioral paeresthesia which have been significantly more reported in the amprenavir

group compared to the indinavir one (53 % versus 37 % and 31 % versus 2 % respectively). Other gastro-intestinal symptoms did not reach statistical significance.

The most frequent adverse events leading to treatment discontinuation were nausea (6 % in the amprenavir arm versus 3 % in the indinavir arm), vomiting (4 % in the amprenavir arm versus 2 % in the indinavir arm) rash (3 % in the amprenavir arm) and diarrhoea (2 % in the amprenavir arm).

Rash

In dose-ranging studies, the incidence of rash was greater in the 1200 mg bid group leading to more discontinuations. Further investigation showed that there was no significant relationship between rash and amprenavir plasma concentrations. On this basis and considering that there might be a risk of resistance occurring when using suboptimal doses, it was not considered necessary to introduce a dose escalation scheme.

Rash was usually mild to moderate, erythematous or maculopapular cutaneous eruptions with or without pruritus, occurring during second week of treatment. Spontaneous resorption usually occurred within 2 weeks. Less than 1 % of severe or life-threatening skin reactions including Stevens-Johnson Syndrome have been reported. The incidence of rash in study CNAA2007 where amprenavir was co-administered with abacavir and efavirenz, was 54 %. This may indicate an additive effect between efavirenz and abacavir. There was no evidence of enhanced toxicity when amprenavir is given in combination with efavirenz and abacavir.

Laboratory findings

Abnormal liver functions were not more frequent with amprenavir in combination with NRTIs than with lamivudine in combination with zidovudine but they were less frequent with amprenavir (37 %) than with indinavir (60 %). Most of the patients (73 %) who reached Grade 3 or 4 transaminase or alkaline phosphatase values were patients with documented co-infection with HBV and/or HCV. In view of the liver toxicity reported in the rat toxicological studies, liver toxicity was monitored during the clinical trials but no significant effect was observed during or after treatment with amprenavir. Based on the review of the two main studies, there was no evidence of enhancement of the low intrinsic hepatotoxicity of amprenavir when other hepatotoxic substances were co-administered.

Abnormal fat redistribution

Based on data collected retrospectively, the incidence of symptoms related to fat redistribution appears low in patients treated with amprenavir. Only one case (buffalo hump) was reported in 113 (< 1 %) antiretroviral naive patients treated with amprenavir in combination with lamivudine/zidovudine (PROAB3001) for a median of 36 weeks (range 0-85). In study PROAB3006 seven cases have been reported over a median duration of 56 weeks (range 0-76). The incidence was significantly higher in patients in the indinavir arm compared to the amprenavir arm (11 % versus versus 3 %). The impact of amprenavir on carbohydrate and lipid metabolism in antiretroviral naive patients will be further evaluated. As for the other protease inhibitors, a class labelling wording has been introduced in the SPC of amprenavir to highlight the potential lipodystrophy and other metabolic disorders associated with combination therapy including protease inhibitors.

Rhabdomyolysis

Macular symptoms were reported in 32 % of patients treated with amprenavir during the main studies as compared to 41 % in the placebo group (PROAB3001) and 42 % in the indinavir group (PROAB3006). Considering that rhabdomyolosis may be considered as a class effect linked to PIs, an adequate class labelling wording has been introduced in the SPC.

Safety in special population

The adverse event profile reported in the two studies in paediatric population was similar to that observed in adult patients. The most common adverse events reported were related to gastrointestinal tract and rash which led to 5 % of discontinuation in both studies.

The incidence of grade 3 or 4 laboratory abnormalities was similar in both studies 9 %. Although some concern related to higher toxicity of amprenavir in young animals (see Part III) the tolerability of amprenavir seemed acceptable. However, data are too limited on children under the age of 4 to recommend the administration of amprenavir in this population.

The safety profile of amprenavir in adults over 65 years old has not been established.

4. Overall conclusions, benefit/risk assessment and recommendations

- The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics. The soft capsules and oral solution are not bioequivalent and therefore cannot be interchanged during treatment on a milligram per milligram basis. Physicochemical aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. However the high amount of propylene glycol in the oral solution raised a concern over its safe use in children.
- Taking into consideration the therapeutic indication of amprenavir, the pharmacological and toxicological profile has been satisfactory defined although there are some concerns related to the toxicity in young animals (probably due to immature metabolising system and influenced by the vehicle) for the use of amprenavir in young children. Due to the suspicion of embryotoxicity with amprenavir in rats, amprenavir should not be given to pregnant women, as indicated in the Summary of Product Characteristics. Carcinogenicity studies are still ongoing and results will be submitted as part of the follow-up measures to be fulfilled by the applicant.
- The inter and intra-variability in the pharmacokinetic parameters is of concern. Although the twice daily regimen was not fully justified to exclude any risk of C_{minss} falling below antiretroviral levels compared to three times daily dosing, 1200 mg bid has been used in the main studies. In children, the recommended dose of 20 mg/kg twice daily of capsules (17 mg/kg three times daily of oral solution) was considered acceptable. However there were some concerns relating to the proposed alternative dosage regimen 15 mg/kg three times daily of capsules (22.5 mg/kg twice daily of oral solution).
- Data on the potential pharmacokinetic interactions with other antiretroviral medicinal products were not extensive but results from ongoing studies will be submitted post-authorisation in order to propose specific dosing recommendations.
- The efficacy data up to 48 weeks showed that amprenavir administered at the dose of 1200 mg bid has an antiviral effect in antiretroviral naive adult patients. Triple therapy including amprenavir and NRTIs was more effective than the double therapy of NRTIs (proportion of patients with HIV RNA < 400 copies/ml = 41 % in amprenavir/lamivudine/zidovudine compared to 3 % in lamivudine/zidovudine). The effects lasted longer although a decline after 16 weeks was apparent in the triple regimen group. Further comparative studies with standard care therapy would be necessary to further evaluate the efficacy of amprenavir in this population.
- In antiretroviral experienced patients, the response was sustained with amprenavir in combination with NRTIs up to 48 weeks. Its efficacy seemed to be lower and less sustained than that of the comparator indinavir (proportion of patients with HIV RNA < 400 copies/ml = 30 % in amprenavir/NRTIs compared to 46 % in indinavir/NRTIs at 48 weeks).
- The efficacy and the safety of amprenavir in patients with advanced HIV-1 disease and in patients treated following failure with PI containing-regimen could not be comprehensively evaluated. Amprenavir seemed to have a favourable resistance profile compared to other protease inhibitors but additional data would be needed to conclude on the use of amprenavir in these patents. Based on results from ongoing studies, amprenavir seemed to contribute to the antiviral effect observed with combination regimens in PI experienced patients. Nevertheless, the design of the studies had some limitations, which do not allow definite conclusions to be drawn on the specific role of amprenavir in such therapy regimen.
- The efficacy and safety of amprenavir in children is supported by data obtained from 268 children. The efficacy pattern is similar in children and adults. Considering the scarcity of the data in children less than 4 years old, amprenavir should not be recommended in this age.

- The solution contains an amount of propylene glycol resulting in a daily intake in excess of the acceptable limit defined by FAO/WHO which poses a potential risk of toxicity, particularly in infants. The review of the literature related to preclinical and clinical data of propylene glycol showed that it is of low toxicity in animals and in humans. When administered at high doses it could promote several toxic effects as central nervous system depression, hyperosmolality, renal toxicity and hemolysis, Patients at risk could be infants and patients with hepatic or renal dysfunction. The data comparing the safety of the solution with that of the capsules (which contain less propylene glycol) in children above 4 years gave some reassurance. Considering the indication, the age limit of 4 years, it was considered that the benefit of treatment with amprenavir outweighs the potential risk of adverse effects.
- Adverse events associated with amprenavir in the clinical setting was mainly related to gastro-intestinal symptoms, rashes and oral/peri-oral paraesthesia. They were generally mild to moderate in severity, early in onset and rarely treatment limiting.

Benefit/risk assessment

The applicant during an oral explanation before the CPMP, focused on the following issues, as previously defined by the CPMP:

- the efficacy activity of amprenavir as compared to that of the currently available protease inhibitors
- the pharmacokinetic data in relation to the proposed dosage regimen/desired therapeutic levels and likely pharmacokinetic interactions.

The potentially favourable resistance profile of this product was discussed but the predictive value of these data and the role of amprenavir in PI experienced patients were considered uncertain. An Ad Hoc group of experts was also convened to discuss the issue. The dose recommendation in adults was adequately addressed by the applicant.

In response to the request of the CPMP, the applicant provided further information particularly to substantiate the potential usefulness of amprenavir in protease inhibitor experienced adults and children.

The CPMP in its concluding assessment of the benefits and risks of amprenavir made the following points:

- There remained concerns over first line treatment of HIV infected adult patients with amprenavir, due to the apparent inferiority versus indinavir. Since no new data were available, the CPMP did not support a first line indication for amprenavir.
- The extensive *in vitro* data provided showed that amprenavir has a distinctive resistance profile which involves different mechanisms from those of other protease inhibitors. In addition, a substantial amount of data and analyses (mostly retrospective) suggested that, for amprenavir, there is a correlation between laboratory data and clinical response. Therefore, amprenavir could be a potential candidate for treatment regimens based on baseline virological testing in PI experienced patients.
- The clinical evidence submitted for amprenavir suggest that the product can have a role in the treatment of patients who have failed previous therapies, for whom there is a medical need. Amprenavir containing salvage regimens (e.g. studies CNAA2007 and ACTG398) have been shown to be effective, but the contribution of amprenavir itself is difficult to establish due to the design of the studies. In addition, the population included in those trials was not homogeneous with regard to PI-experience and level of virological failure. The CPMP requested the applicant to conduct a prospective clinical trial of amprenavir in PI-experienced patients to clearly establish the efficacy of the product in this population. The protocol of this study submitted by the applicant was further discussed during the hearing held before the CPMP. As part of the specific obligation to be fulfilled, the results of this study will be submitted and will form the basis of the annual re-assessment of the benefit/risk profile.

- The drug-drug interaction information has been expanded so as to justify the dosage of amprenavir when used in combination with other antiretrovirals, likely to occur in the proposed indication. Preliminary data showed that the combination with ritonavir may be of interest in term of pharmacokinetic exposure. However, the available information is still preliminary and should be completed on an on-going basis, particularly in relation to efficacy and safety. This is particularly relevant in relation to children.
- The three times a day dosage in children using the oral solution was accepted. Considering the high amount of propylene glycol, the CPMP agreed that the oral solution could only be considered as a temporary stage during amprenavir therapy. Therefore children should switch to the capsules as soon as the child is able to swallow them. This, as well as the potential dangers of the propylene glycol, which should be carefully monitored, are explained in the Summary of Product Characteristics.

RECOMMENDATION

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk profile of Agenerase was favourable for use in combination with other antiretroviral agents in the treatment of protease inhibitor (PI) experienced HIV-1 infected adults and children above the age of 4 years. The choice of amprenavir should be based on individual viral resistance testing and treatment history of patients (see section 5.1). In protease inhibitor naive patients, Agenerase is less effective than indinavir.